Clinical Neurophysiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Clinical correlates of rapid eye movement sleep without atonia in Parkinson's disease

Yun Shen [a,1], Kang-ping Xiong [a,1], Jie Li [a], Cheng-jie Mao [a], Jing Chen [a], Pei-cheng He [a], Jun-ying Huang [a], Yong-ping Dai [a], Wei-feng Luo [a], Chun-feng Liu [a,b,*]

[a] Department of Neurology, Jiangsu Key Laboratory of Translational Research and Therapy for Neuro-Psycho-Diseases and The Second Affiliated Hospital of Soochow University, Soochow University, Suzhou 215004, China
[b] Institute of Neuroscience, Soochow University, Suzhou 215123, China

A R T I C L E I N F O

Article history:
Accepted 10 September 2014
Available online xxxx

Keywords:
Parkinson's disease
Rapid eye movement sleep
Muscle atonia
Polysomnography

H I G H L I G H T S

- Parkinson's disease (PD) severity was worse in patients with more rapid eye movement sleep without atonia (RWA).
- Tonic RWA was more closely correlated with PD severity than phasic RWA.
- Our new method of RWA analysis may provide a graded index that reflects PD progression.

A B S T R A C T

Objective: The aim of the present study was to investigate the relationship between rapid eye movement (REM) sleep without atonia (RWA) and Parkinson's disease (PD) progression.
Methods: We quantified tonic and phasic RWA by performing polysomnography in 198 PD patients. We then correlated the extent of RWA with clinical patient characteristics.
Results: PD patients were categorized into quartiles of tonic and phasic RWA. We found that patients with more RWA tended to be older and have longer PD duration, a greater likelihood of REM sleep behavior disorder (RBD), more advanced Hoehn & Yahr (H&Y) stage, a higher dose of parkinsonian medication, poorer cognitive performance, worse quality of life, and more severe sleep disturbance. After adjusting for age, sex, and PD duration, patients in the highest two RWA quartile were more likely to have severe PD (H&Y stage $\geqslant$ 3.0) than those in the lowest RWA quartile.
Conclusions: These findings provide evidence that RWA, especially with regard to tonic muscle activity, is associated with PD severity.
Significance: Further studies are warranted to determine the importance and utility of assessing RWA to evaluate sleep in PD patients.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal muscle atonia during REM sleep, leading to dream-enactment behavior. RBD has been detected in up to 60% of patients with Parkinson's disease (PD) (Sixel-Doring et al., 2011).

REM sleep without atonia (RWA) is a requisite diagnostic feature of RBD evidenced by either excessively sustained or intermittent elevation of electromyogram (EMG) tone or excessive phasic EMG activity on polysomnography (PSG). One common method of manually scoring muscle activity in RBD research is to distinguish between phasic and tonic EMG activity in submental EMG recordings. RWA may also be observed incidentally on PSG without dream-enactment behavior, even in normal individuals (Ferri et al., 2012). Similar to RBD, RWA can be a precursor of neurodegenerative diseases, mainly synucleinopathies (McCarter et al., 2012).

* Corresponding author at: Department of Neurology, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215004, China. Tel.: +86 512 67783307; fax: +86 512 68284303.
E-mail address: liucf@suda.edu.cn (C.-f. Liu).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.clinph.2014.09.014
1388-2457/

Compared with PD patients without RBD, those with RBD have higher percentages of tonic and phasic RWA (Gong et al., 2014) and more severe motor and non-motor PD manifestations (Arnulf, 2012). Still, the relationships among the clinical characteristics of RWA and PD are not yet clear, especially in PD patients without RBD symptoms who show RWA on PSG. One study, which focused only on phasic RWA, reports that RWA is associated with more severe motor symptoms in PD patients (Bliwise et al., 2010). Another study reports that tonic and phasic RWA increase over time due to underlying progressive pathological processes in brainstem structures that modulate REM sleep in idiopathic RBD patients (Iranzo et al., 2009). However, these studies largely focused on the coexistence of RBD and PD, and little is known about the progression of RWA over time in PD patients.

In the present study, we assessed RWA in a large unselected sample of PD patients using a cross-sectional design. By excluding patients with dream-enactment behavior, we were able to focus on muscle tone during REM sleep as a putative dynamic marker of brainstem neurodegeneration that correlates with other clinical and sleep characteristics.

2. Methods

2.1. Subjects

Patients with PD were recruited between December 2007 and September 2013 from the Center of Parkinsonism and Movement Disorders at the Second Affiliated Hospital of Soochow University. Ethics approval was obtained from the hospital's Ethical Committee, and all patients gave written informed consent. The inclusion criteria for PD were based on the UK Parkinson's Disease Society Brain Bank clinical diagnosis criteria (Hughes et al., 1992). Subjects were excluded if they had a psychiatric disease or severe dementia or if they were not able to successfully complete clinical testing or PSG (e.g., patients without REM sleep). Patients who were taking selective serotonin re-uptake inhibitors, selective noradrenaline re-uptake inhibitors, or clonazepam were excluded from the study, as these medications are associated with altered EMG activity (Lapierre and Montplaisir, 1992; Winkelman and James, 2004). Subjects taking medications for PD were allowed to continue taking the medications as usual. Drug dosages were converted to levodopa dosage equivalents (LEDs) (Tomlinson et al., 2010).

All patients underwent a clinical evaluation including a comprehensive neurological examination, the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn & Yahr (H&Y) scale, the Montreal Cognitive Assessment (MOCA, Beijing Version), and the PD Quality of Life Questionnaire (PDQ). Patients with nocturnal dream-enactment behavior history before PSG were considered to have clinically probable RBD (pRBD) (Boeve, 2010).

2.2. Sleep assessment

All subjects underwent one night of continuous video-PSG monitoring using standard methods in the sleep laboratory. Digital recordings included electroencephalogram (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, and O2-A1), chin EMG, electrooculogram, electrocardiogram, and measurements of snoring, respiratory effort using piezoelectric belts over the chest and abdomen, airflow at the nose and mouth using thermocouples, and pulse oximetry.

PSGs were visually scored by experienced PSG technologists according to the American Academy of Sleep Medicine Guidelines (Medicine, 2007). RWA was scored according to a previously described visual quantitative method (Montplaisir et al., 2010). Specifically, each 20-s REM sleep epoch was scored as tonic depending on the presence of chin EMG activity with an amplitude of at least twice that of background activity or >10 μV for more than 50% of each epoch. For scoring phasic EMG density, the percentage of 2-s mini epochs of REM sleep containing phasic EMG events was calculated. These phasic EMG events were defined as any burst of EMG activity lasting 0.1–10 s with an amplitude exceeding four times that of background activity. All snoring and arousals based on respiratory events were carefully eliminated from REM tone quantification.

2.3. Statistical analyses

SPSS software version 17.0 (Chicago, IL, USA) was used for statistical analyses. Tonic and phasic EMG densities were not normally distributed and are therefore described by percentiles. Because we wanted to analyze the relationships between RWA and clinical characteristics in PD patients, all patients were categorized into quartiles of tonic or phasic EMG densities using the 25th, 50th, and 75th percentiles as cut-offs. Descriptive data are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage) where appropriate. All comparisons were performed using analysis of covariance (ANCOVA) or Kruskal–Wallis analysis of variance (ANOVA). Nonconditional logistic regression analysis was performed to determine the risk of severe PD (H&Y stage ⩾ 3.0) with increased EMG activity controlling for age, gender, and PD duration. Odds ratios (ORs) and 95% confidence intervals (CIs) of severe PD were calculated for each RWA quartile using the lowest quartile as a reference. Trends in ORs for severe PD across RWA quartiles were determined considering RWA quartile as an ordinal variable. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. Demographics and clinical characteristics

A total of 209 PD patients were investigated, but data from 11 patients were not included due to technical artifacts on chin EMGs. The final cohort consisted of 127 males and 61 females with a mean age of 65.2 ± 10.3 years (range, 33–86), mean PD duration of 50.7 ± 41.8 months (range, 4–250), mean H&Y stage of 2.2 ± 0.8 (range, 1–4), and mean LED of 335.6 ± 301.8 mg/day (range, 0–1500.0). Ninety-nine patients (50%) were classified as having pRBD, and 31 patients (15.7%) showed an index of respiratory events (apnea–hypopnea index (AHI)) >15.

Patients were categorized into quartiles of tonic or phasic RWA. The quartiles of tonic RWA were T1 (<1.2%), T2 (⩾1.2% to <6.9%), T3 (⩾6.9% to <23.1%), and T4 (⩾23.1%). The quartiles of phasic RWA were P1 (<5.1%), P2 (⩾5.1% to <15.7%), P3 (⩾15.7% to <36.5%), and P4 (⩾36.5%).

Demographics and clinical characteristics of PD patients in the tonic and phasic RWA quartiles are summarized in Tables 1 and 2. We found that patients in higher RWA quartiles tended to be older and to exhibit a greater likelihood of pRBD, longer PD duration, more advanced H&Y stage, higher dose of parkinsonian medication, lower cognitive performance, and worse quality of life. There were no significant differences among quartiles in family history of PD or UPDRS score.

3.2. PSG parameters

PSG parameters of PD patients in the tonic and phasic RWA quartiles are summarized in Tables 3 and 4. Patients in higher RWA quartiles had higher and lower percentages of stage 1 (NREMS1) and stage 2 (NREMS2) sleep, respectively. There were no significant differences among quartile groups for most PSG

Please cite this article in press as: Shen Y et al. Clinical correlates of rapid eye movement sleep without atonia in Parkinson's disease. Clin Neurophysiol (2014), http://dx.doi.org/10.1016/j.clinph.2014.09.014

Table 1
Demographics and clinical characteristics of PD patients by tonic RWA quartile.

	T1	T2	T3	T4	*P*-value
Tonic %	[<1.2]	[1.2–6.9]	[6.9–23.1]	[>23.1]	–
N	47	52	50	49	–
Age (y)	62.0 ± 9.9[a]	63.0 ± 11[b]	66.0 ± 10.1	69.5 ± 8.3	0.001
Male *n* (%)	25 (53.2)	36 (69.2)	29 (58.0)	37 (75.5)	0.085
Family history *n* (%)	3 (6.4)	3 (5.8)	3 (6.0)	3 (6.1)	0.999
pRBD *n* (%)	11 (23.4)[a,d]	19 (36.5)[b,e]	29 (58.0)[c]	40 (81.6)	0.000
PD duration (m)	40.6 ± 30.9[a]	47.7 ± 36.1[b]	52.1 ± 46.5	61.4 ± 48.9	0.044
H&Y stage	1.8 ± 0.5[a,d]	2.0 ± 0.7[b,e]	2.5 ± 0.9	2.6 ± 0.6	0.000
H&Y stage $\geqslant$ 3.0 *n* (%)	3 (6.4)[a,d]	12 (23.1)	18 (36.0)	21 (42.9)	0.000
LED (mg/d)	274.7 ± 320.8[a]	288.1 ± 251.7[b]	341.9 ± 310.9	441.3 ± 312.2	0.046
Total UPDRS score	34.7 ± 15.2	38.8 ± 16.8	38.4 ± 18.0	45.9 ± 16.4	0.082
MOCA score	26.3 ± 2.9[a]	25.0 ± 2.6[b]	24.8 ± 3.4[c]	22.7 ± 3.6	0.000
PDQ score	154.0 ± 19.5[a]	146.8 ± 25.5[b]	148.1 ± 36.3[c]	127.9 ± 18.6	0.004

Abbreviations: H&Y = Hoehn & Yahr; LED = levodopa equivalent dose; m = months; MOCA = Montreal Cognitive Assessment scale; *n* = number; PDQ = Parkinson's Disease Quality of Life questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; y = years. Values are mean ± standard deviation or frequency (percentage).
[a] Significant difference between groups 1 and 4.
[b] Significant difference between groups 2 and 4.
[c] Significant difference between groups 3 and 4.
[d] Significant difference between groups 1 and 3.
[e] Significant difference between groups 2 and 3.

Table 2
Demographics and clinical characteristics of PD patients by phasic RWA quartile.

	P1	P2	P3	P4	*P*-value
Phasic %	[<5.1]	[5.1–15.7]	[15.7–36.5]	[>36.5]	–
N	48	51	50	49	–
Age (y)	61.5 ± 10.8[a,d]	63.6 ± 11.8[b,e]	67.8 ± 8.8	67.6 ± 8.2	0.004
Male *n* (%)	28 (58.3)	37 (72.5)	28 (58.0)	33 (67.3)	0.346
Family history *n* (%)	3 (6.3)	3 (5.9)	3 (6.0)	3 (6.1)	0.999
pRBD *n* (%)	9 (18.8)[a,d]	18 (35.3)[b,e]	36 (58.0)	36 (73.5)	0.000
PD duration (m)	40.6 ± 28.4[a]	46.1 ± 37.6[b]	49.4 ± 44.3[c]	65.9 ± 50.0	0.020
H&Y stage	1.8 ± 0.6[a,d]	2.1 ± 0.6[b]	2.3 ± 1.0	2.6 ± 0.6	0.000
H&Y stage $\geqslant$ 3.0 *n* (%)	5 (10.4)[a]	10 (19.6)	16 (32.0)	23 (46.9)	0.002
LED (mg/d)	206.7 ± 222.6[a]	305.7 ± 310.7[b]	315.3 ± 307.8[c]	503.7 ± 285.6	0.000
Total UPDRS score	36.0 ± 18.5	39.3 ± 15.5	40.1 ± 18.7	44.1 ± 15.2	0.288
MOCA score	26.6 ± 2.5[a,d]	25.1 ± 2.8	23.8 ± 3.6	23.7 ± 3.6	0.001
PDQ score	151.3 ± 24.8[a]	150.1 ± 22.7[b]	144.0 ± 38.9	134.5 ± 21.2	0.068

Abbreviations: H&Y = Hoehn & Yahr; LED = levodopa equivalent dose; m = months; MOCA = Montreal Cognitive Assessment scale; *n* = number; PDQ = Parkinson's Disease Quality of Life questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale; y = years.
Values are mean ± standard deviation or frequency (percentage).
[a] Significant difference between groups 1 and 4.
[b] Significant difference between groups 2 and 4.
[c] Significant difference between groups 3 and 4.
[d] Significant difference between groups 1 and 3.
[e] Significant difference between groups 2 and 3.

measures, including total sleep time (TST), sleep efficiency (SE), sleep latency (SL), REM sleep latency (REML), the percentage of slow-wave sleep (SWS), the percentage of REM sleep (REMS), AHI, or oxygen desaturation index (ODI).

3.3. Regression analysis

After adjusting for age, sex, and PD duration, we found that higher tonic and phasic RWA quartiles contained more patients with severe PD (Table 5). That is, PD patients in the highest two RWA quartile were more likely to have severe PD (H&Y stage $\geqslant$ 3.0) than those in the lowest quartile.

4. Discussion

In the present study, by categorizing PD patients into RWA quartiles, we found an association between enhanced muscle tone during REM sleep and PD severity. To our knowledge, this is the first study to employ this method of RWA analysis.

Previous investigations have focused on relationships between the clinical features of PD and the coexistence of RBD or other sleep features. For instance, PD patients with RBD were found to be older, to have longer durations of PD and higher doses of antiparkinsonian medication, and to experience more severe levels of disability (Lee et al., 2010). In addition, a recent PSG-based study of an unselected cohort of sleep-disturbed PD patients reports that patients with RBD (but not necessarily a history of RBD) exhibit more advanced H&Y stage as well as more falls, fluctuations, and psychiatric comorbidities (Sixel-Doring et al., 2011).

In accordance with these previous findings, we found that higher RWA quartiles tended to include patients with a greater likelihood of pRBD, longer PD duration, more advanced H&Y stage, higher dose of parkinsonian medications, poorer cognitive performance, worse quality of life, and greater sleep disturbance. One potential explanation of these findings is that because the loss of REM atonia is an essential hallmark of RBD, greater EMG activity during REM sleep could be interpreted as more severe RBD. Besides, the presence of RBD in PD patients was associated with

Table 3
PSG parameters of PD patients by tonic RWA quartile.

	T1	T2	T3	T4	*P*-value
TST (min)	346.0 ± 118.1	350.7 ± 94.1	350.4 ± 94.7	326.9 ± 114.9	0.638
SE (%)	61.1 ± 27.0	60.6 ± 25.1	63.7 ± 20.7	59.8 ± 19.1	0.850
SL (min)	13.5 (4.4–47.9)	14.0 (8.0–26.5)	13.8 (7.9–27.0)	20.5 (4.9–38.4)	0.735[*]
REML (min)	146.0 ± 95.6	148.8 ± 87.9	141.0 ± 83.4	179.6 ± 106.9	0.167
NREMS1 (%)	22.3 ± 13.1[a,d]	26.9 ± 11.8[b]	30.0 ± 14.6[c]	39.4 ± 22.4	0.000
NREMS2 (%)	53.1 ± 16.9[a,d]	47.2 ± 12.2[b]	42.7 ± 13.0[c]	35.4 ± 17.4	0.000
SWS (%)	11.4 (4.8–18.3)	10.5 (1.3–15.1)	9.4 (1.3–16.4)	8.4 (2.1–18.3)	0.886[*]
REMS (%)	14.9 ± 7.2	15.4 ± 6.6	16.4 ± 7.4	13.2 ± 7.9	0.136
AHI (/h)	1.1 (0.0–6.0)	3.3 (0.3–10.7)	1.6 (0.0–7.5)	1.3 (0.0–6.7)	0.469[*]
ODI (/h)	1.1 (0.1–5.7)	2.2 (0.4–7.4)	1.7 (0.2–4.6)	1.2 (0.2–6.7)	0.806[*]
PLMSI (/h)	2.7 (0.0–27.5)[a,d]	9.9 (1.1–34.6)	11.7 (5.0–57.9)	30.6 (1.1–60.3)	0.025[*]

Abbreviations: PSG = polysomnography; TST = total sleep time; SE = sleep efficiency; SL = sleep latency; REML = rapid eye movement latency; NREMS = non-rapid eye movement sleep; SWS = slow-wave sleep; REMS = rapid eye movement sleep; AHI = apnea–hypopnea index; ODI = oxygen desaturation index; PLMSI = index of periodic leg movements during sleep. [e]Significant difference between groups 2 and 3.
Values are mean ± standard deviation or median (interquartile range).
[*] Kruskal–Wallis ANOVA.
[a] Significant difference between groups 1 and 4.
[b] Significant difference between groups 2 and 4.
[c] Significant difference between groups 3 and 4.
[d] Significant difference between groups 1 and 3.

Table 4
PSG parameters of PD patients by phasic RWA quartile.

	P1	P2	P3	P4	*P*-value
TST (min)	340.4 ± 89.9	355.9 ± 116.1	346.2 ± 98.3	331.3 ± 115.7	0.700
SE (%)	61.6 ± 24.8	59.6 ± 27.0	62.3 ± 20.7	61.6 ± 19.4	0.945
SL (min)	15.5 (5.5–41.0)	12.5 (6.0–26.5)	17.5 (10.3–27.5)	14.0 (4.5–33.5)	0.484[*]
REML (min)	145.0 ± 94.4	142.3 ± 81.1	144.0 ± 87.6	184.2 ± 108.5	0.157
NREMS1 (%)	22.5 ± 12.9[a,d]	26.5 ± 12.5[b]	32.3 ± 16.1	37.3 ± 21.7	0.000
NREMS2 (%)	52.7 ± 16.6[a,d,f]	45.0 ± 12.8[b]	43.0 ± 14.5	37.7 ± 17.5	0.000
SWS (%)	11.5 (3.8–18.1)	11.0 (3.9–20.0)	7.9 (1.0–14.9)	8.2 (2.4–17.7)	0.568[*]
REMS (%)	14.6 ± 7.8	16.8 ± 5.9	14.5 ± 6.8	14.1 ± 8.5	0.255
AHI (/h)	1.9 (0.3–7.6)	2.4 (0.3–17.5)	0.7 (0.0–5.3)	1.7 (0.0–6.8)	0.201[*]
ODI (/h)	1.1 (0.4–4.9)	2.2 (0.3–9.5)	0.9 (0.0–4.6)	1.4 (0.2–6.2)	0.507[*]
PLMSI (/h)	4.6 (1.0–25.8)	4.8 (0.0–41.6)	14.0 (5.6–60.6)	12.6 (0.4–46.7)	0.136[*]

Abbreviations: PSG = polysomnography; TST = total sleep time; SE = sleep efficiency; SL = sleep latency; REML = rapid eye movement latency; NREMS = non-rapid eye movement sleep; SWS = slow-wave sleep; REMS = rapid eye movement sleep; AHI = apnea–hypopnea index; ODI = oxygen desaturation index; PLMSI = index of periodic leg movements during sleep.
Values are mean ± standard deviation or median (interquartile range). [c]Significant difference between groups 3 and 4. [e]Significant difference between groups 2 and 3.
[*] Kruskal–Wallis ANOVA.
[a] Significant difference between groups 1 and 4.
[b] Significant difference between groups 2 and 4.
[d] Significant difference between groups 1 and 3.
[f] Significant difference between groups 1 and 2.

Table 5
ORs and 95% CIs of severe PD (H&Y stage ⩾ 3.0) associated with RWA quartile.

	Unadjusted	*P*-value	Adjusted[a]	*P*-value
T1	1.00 (reference)	–	1.00 (reference)	–
T2	4.3 (1.1–16.8)	0.037	6.4 (1.3–32.3)	0.026
T3	8.2 (2.1–32.3)	0.002	11.1 (2.3–55.2)	0.003
T4	12.4 (3.2–47.6)	<0.001	13.2 (2.6–67.5)	0.002
P for trend		<0.001		0.001
P1	1.00 (reference)	–	1.00 (reference)	–
P2	2.8 (0.7–10.3)	0.129	2.3 (0.7–7.6)	0.170
P3	5.5 (1.5–19.5)	0.009	4.6 (1.5–14.4)	0.010
P4	5.5 (1.6–19.6)	0.008	6.9 (2.3–21.2)	0.001
P for trend		<0.001		0.004

Abbreviations: OR = odds ratio; CI = confidence interval; H&Y = Hoehn & Yahr.
[a] Covariates for adjustment include age, gender, and PD duration.

more severe PD. Therefore, there is the relationship between greater EMG activity and PD progression.

In addition, we used the H&Y scale to identify patients with severe PD in order to examine whether a specific amount of muscle activity during REM sleep is associated with PD progression. H&Y is a simple, commonly used scale that stages patients based on their current level of function. Most importantly, it can be used to categorize PD patients and to capture critical aspects of PD progression (Goetz et al., 2004). After a patient reaches stage 3, the progression of PD motor impairment accelerates, and PD patients have higher risks of dementia and reduced survival (Roos et al., 1996; Goetz et al., 2000). One recent study reported that median RWA was significantly greater in patients at H&Y stage 3 than in patients at H&Y stages 1 and 2 (Chahine et al., 2014). Therefore, patients at H&Y stage 3 or higher can be considered to have severe PD. By comparing the numbers of patients with severe PD in different quartiles and calculating ORs, we were able to identify a relationship between greater RWA and PD severity. That is, PD patients in the highest RWA quartile were more likely to have severe PD (H&Y scale ⩾ 3.0) than those in the lowest quartile.

The pathological reason for the link between RWA and PD severity is not clear. One possibility is that RWA is related to the temporal sequence of synuclein deposition described by Braak's staging hypothesis (Braak et al., 2004; Boeve, 2013); however, the mechanisms underlying RWA remain poorly understood. A recent study using neuromelanin-sensitive magnetic resonance

imaging provides evidence that the locus coeruleus/subcoeruleus is involved in atonia during REM sleep in PD patients (Garcia-Lorenzo et al., 2013). At the same time, the site and severity of brain lesions determine the occurrence of simple or complex behaviors (Boeve et al., 2007). Hence, RWA and RBD might manifest at H&Y stage 2 or 3 due to Lewy body deposition or neurodegeneration affecting the brainstem. These events occur prior to basal ganglia and cortical degeneration, which cause motor and cognitive impairments (McCarter et al., 2012). As PD continues to advance, the degeneration of specific brain nuclei may accelerate over time. Thus, RWA can occur in the early stages of PD and worsen as the disease progresses.

Our results show that the ORs of severe PD in tonic RWA quartiles were higher than those in phasic RWA quartiles. We speculate that tonic RWA more strongly correlates with PD status than phasic RWA due to differences in the regulatory mechanisms of the two EMG activities. Tonic RWA may reflect degeneration of the sublaterodorsal nucleus (Gjerstad et al., 2008), whereas phasic RWA may depend on activation of locomotor generators during sleep and alterations of intermediate ventromedial medulla pathways (Boeve et al., 2007). Moreover, patients with idiopathic RBD who subsequently developed PD had increased tonic but not phasic RWA at baseline compared to those who remained disease-free (Postuma et al., 2010). We had insufficient power to perform subgroup analyses, however, in part due to our wide CI ranges; therefore, a larger number of patients would need to be studied to perform such assessments.

Currently, there is no consensus on quantitative scoring rules and EMG activity cut-off values for RBD diagnosis. Instead, the presence of RWA is mostly based on the subjective qualitative impression of the individual scorer. Montplaisir et al. first sought to determine cut-off values for phasic and tonic chin EMG activity, proposing cut-off values for RBD diagnosis of 30% tonic activity and 15% phasic activity. According to these criteria, only 42 patients (21.2%) in the tonic group and 100 patients (50.5%) in the phasic group would be diagnosed as having RBD in our study (Montplaisir et al., 2010). In the present study, before performing PSG, 99 of 198 PD patients (50.0%) were considered to have pRBD, which is similar to the percentage seen in the phasic group. Hence, phasic RWA may distinguish between individuals with and without RBD. By contrast, a large of proportion of patients were considered to have pRBD, but their tonic RWA failed to meet the PSG criteria for RBD. There are four possible reasons for this observation. First, the cut-offs for tonic RWA in PD patients might be different from those originally developed for idiopathic RBD patients. In addition, antiparkinsonian medications and the nature of PD progression can affect tonic RWA (Garcia-Borreguero et al., 2002). Second, in order to evaluate RWA in a large unselected sample of PD patients, we did not exclude patients with an AHI > 15, which is different from the methods employed by Montplaisir et al. In that study, nonspecific RWA due to upper airway muscle dysfunction may have influenced true tonic chin EMG activity, which may have affected the analysis. Third, like previous studies (Zhang et al., 2008; Zhou et al., 2014), we observed lower EMG activity in Chinese patients with RBD compared with RBD patients of European descent. We speculate that ethnic variations may be a reason for this discrepancy, although further studies are needed confirm this possibility. Finally, we obtained information related to pRBD through clinical interviews rather than questionnaires, which may have impacted the accuracy of this data. Several other mimicking disorders must be distinguished from RBD, including nightmares, sleepwalking, sleep terrors, nocturnal seizures, obstructive sleep apnea with atypical arousals from REM sleep, nocturnal panic disorder, delirium, and others.

Furthermore, our study provides additional evidence that patients with PD show abnormal sleep patterns. Specifically, PD patients with increased RWA had a higher percentage of stage 1 sleep and a lower percentage of stage 2 sleep, which is in line with previous reports (Shpirer et al., 2006; Yong et al., 2011). Collectively, the existing data suggest that sleep disturbances increase as PD progresses.

It is important to note some limitations of this study. First, the sample size was not sufficiently large for subgroup analyses. Second, because this was a cross-sectional study, we could not correlate changes in RWA with PD progression over time. Third, our sample was not reflective of a natural cohort of patients at various stages of PD. Some patients (i.e., those at H&Y stage 5) were not able to undergo PSG, but we can deduce that they had higher RWA.

In summary, the results of our study indicate that RWA is associated with the severity of PD. Thus, RWA may be a useful index that reflects microstructural brainstem changes involved in PD progression.

Acknowledgments

A project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions. Jiangsu Provincial Special Program of Medical Science (BL2014042); Suzhou Science and Technology Development Program (SZS201205); Suzhou Clinical Key Disease Diagnosis and Treatment Technology Foundation (LCZX201304).

Conflict of interest: The authors report no conflicts of interest.

References

Arnulf I. REM sleep behavior disorder: motor manifestations and pathophysiology. Mov Disord 2012;27:677–89.

Bliwise DL, Trotti LM, Greer SA, Juncos JJ, Rye DB. Phasic muscle activity in sleep and clinical features of Parkinson disease. Ann Neurol 2010;68:353–9.

Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci 2010;1184:15–54.

Boeve BF. Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. Lancet Neurol 2013;12:469–82.

Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007;130:2770–88.

Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121–34.

Chahine LM, Kauta SR, Daley JT, Cantor CR, Dahodwala N. Surface EMG activity during REM sleep in Parkinson's disease correlates with disease severity. Parkinsonism Relat Disord 2014;20:766–71.

Ferri R, Bruni O, Fulda S, Zucconi M, Plazzi G. A quantitative analysis of the submentalis muscle electromyographic amplitude during rapid eye movement sleep across the lifespan. J Sleep Res 2012;21:257–63.

Garcia-Borreguero D, Caminero AB, De La Llave Y, Larrosa O, Barrio S, Granizo JJ, et al. Decreased phasic EMG activity during rapid eye movement sleep in treatment-naive Parkinson's disease: effects of treatment with levodopa and progression of illness. Mov Disord 2002;17:934–41.

Garcia-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain 2013;136:2120–9.

Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry 2008;79:387–91.

Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004;19:1020–8.

Goetz CG, Stebbins GT, Blasucci LM. Differential progression of motor impairment in levodopa-treated Parkinson's disease. Mov Disord 2000;15:479–84.

Gong Y, Xiong KP, Mao CJ, Shen Y, Hu WD, Huang JY, et al. Clinical manifestations of Parkinson disease and the onset of rapid eye movement sleep behavior disorder. Sleep Med 2014;15:647–53.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.

Iranzo A, Ratti PL, Casanova-Molla J, Serradell M, Vilaseca I, Santamaria J. Excessive muscle activity increases over time in idiopathic REM sleep behavior disorder. Sleep 2009;32:1149–53.

Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 1992;42:1371–4.
Lee JE, Kim KS, Shin HW, Sohn YH. Factors related to clinically probable REM sleep behavior disorder in Parkinson disease. Parkinsonism Relat Disord 2010;16:105–8.
McCarter SJ, St Louis EK, Boeve BF. REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. Curr Neurol Neurosci Rep 2012;12:182–92.
The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2044–51.
Postuma RB, Gagnon JF, Rompre S, Montplaisir JY. Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 2010;74:239–44.
Roos RA, Jongen JC, van der Velde EA. Clinical course of patients with idiopathic Parkinson's disease. Mov Disord 1996;11:236–42.
Shpirer I, Miniovitz A, Klein C, Goldstein R, Prokhorov T, Theitler J, et al. Excessive daytime sleepiness in patients with Parkinson's disease: a polysomnography study. Mov Disord 2006;21:1432–8.
Sixel-Doring F, Trautmann E, Mollenhauer B, Trenkwalder C. Associated factors for REM sleep behavior disorder in Parkinson disease. Neurology 2011;77:1048–54.
Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649–53.
Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27:317–21.
Yong MH, Fook-Chong S, Pavanni R, Lim LL, Tan EK. Case control polysomnographic studies of sleep disorders in Parkinson's disease. PLoS One 2011;6:e22511.
Zhang J, Lam SP, Ho CK, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? Sleep 2008;31:1179–85.
Zhou J, Zhang J, Du L, Li Z, Li Y, Lei F, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case–control study. Sleep Med 2014;15:654–60.

Please cite this article in press as: Shen Y et al. Clinical correlates of rapid eye movement sleep without atonia in Parkinson's disease. Clin Neurophysiol (2014), http://dx.doi.org/10.1016/j.clinph.2014.09.014